PATENT SPECIFICATION

NO DRAWINGS

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COMPLETE SPECIFICATION

Polymeric Coating of Aspirin

I, MINISTER OF TECHNOLOGY, London, a British subject, do hereby declare the invention, for which I pray that a patent may be granted to me, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to the provision of coatings of aspirin polymer on aspirin and related compounds, for example, its pharmaceutically-acceptable salts.

Over the last thirty years, much work has been done on providing coatings for tablets of aspirin of (acetylsalicyclic acid) and similar analgesic drugs. Raw aspirin has several shortcomings; it is released into the system at too fast a rate so that in areas of the system where local concentrations of aspirin are too high, there is good evidence to show that its absorption through the walls of the stomach and intestine gives rise to side effects, such as lesions and haemorrhages. Evidence has indicated that damage to the vessel wall during dissolution of the aspirin is more pronounced in the stomach than in the intestine, possibly because in the latter mixing is more thorough and a large surface area is available for absorption. A reduction of the initial rate of solution of aspirin in the stomach should therefore minimise side effects by ensuring that more absorption of the aspirin takes place in the intestine and less in the stomach.

Clearly, then the problem was to control the rate of release of medicament in the system, suitably by the use of a timed release agent, usually a compound of a fatty, waxy or cellulosic nature. Early attempts at lowering the initial rate of solution, generally employed one of two main techniques (a) formation of an insoluble derivative of aspirin, or (b) application of an enteric coating which resists gastric secretions but which dissolves or disintegrates in the intestine where the pH is higher. The disadvantages of the former technique are the invariably high preparation expenses and the failure of part of the administered dose to be absorbed. When coated tablets are used the whole aspirin tablet is coated and disintegration in the stomach is prevented. The period that elapses before the tablet passes to the intestine is variable and may be as long as eight hours.

Ideally a coating should allow rapid disintegration followed by limited dissolution (10 to 20% by weight) of the tablet in the stomach, with the remainder of the aspirin dissolving in the intestine over a period of two hours. Other desirable features are that it should be inexpensive, easy to apply and non-toxic. It is preferable to apply such a coating to the individual aspirin crystallites rather than to the tablet as a whole.

It has now been found that aspirin polymer is a very satisfactory coating material being itself analgesic and avoiding the introduction of extraneous materials.

The present invention therefore provides tablets or crystallites of aspirin coated with aspirin polymer. The invention also provides processes for the formation of such coatings on the surface of the tablets or crystallites.

Aspirin polymer probably comprises polysalicylic anhydrides of the general formula $H(O.C_6H_4.CO)_nOH$ where n is an integer (J.C.S., *1951*, p 201 to 208). The preferred polymers for use in the process of the invention are those of the general formula in which n=2 to 6.

Either the whole tablet can be coated or individual crystallites can be provided with coatings and these can then be formed into tablets.

Aspirin can conveniently be coated with a layer of aspirin polymer by one of two methods. The first method is the polymerisation of the surface of aspirin crystallites or tablet by heat *in situ*. In this way a thin layer of polymer is formed on the surface.

Prolonged heating at lower temperatures (Example 2) appeared to be more effective than short periods at elevated temperatures (Example 1), (see Table 1). At the higher temperature the heating time had to be short

[*Price 4s. 6d.*]

so as to avoid distortion or gross melting of the pellet.

In one embodiment of the heating process samples of aspirin pellets placed on a tray were heated in an electrically-heated thermostatically controlled furnace for the required time; shorter times of heating were obtained by passing the pellet through a similar furnace arranged vertically.

This method gave a superficial layer of polymer, which reduced the dissolution rate by about 40%.

If, however, this technique is used on aspirin crystallites, where distortion of shape and considerably more melting can be tolerated, e.g. using a fluidised bed technique operating near the melting point of aspirin, then a greater reduction in the rate of dissolution in the test solution can be expected.

The coating of the polymer may also be applied to a pellet or crystallite of aspirin from a solution of the polymer in a volatile solvent by methods known in the art of applying coatings to pharmaceutical products such as, tablets, pills or the like, for instance by immersion in a solution of the polymer and allowing the solvent to evaporate or by spraying the tablets with the solution. The application of a coating of the polymer to a pellet surface by immersing the pellets in a solution of the polymer resulted in a considerable reduction in the rate of solution (see Table 2). Suitable solvents for this method are those which are chemically inert to both the polymer and aspirin and which dissolve the polymer but have no or substantially no solvent action on the aspirin. Good control was possible (compare Examples 4, 5, 6). The most effective treatment was to dip the pellet into the polymer solution five times, drying in air after each dip. This resulted in a reduction in the rate of solution of 80% over a period of 4½ hours. To investigate the effect of mixing a portion of powdered polymer with aspirin crystals, a pellet containing 5% polymer was pressed and then tested in the usual way (Example 6); there was, however, only a very small decrease in the solution rate.

Other comparative results, obtained with tablets coated by conventional techniques, are also given in Table 2.

The pellets used were of high density (98% single crystal value) and there was no disintegration during the experiments. In dissolution tests these may be regarded, therefore, as behaving like individual aspirin crystals. It was possible to prepare them with close reproducibility of surface area to weight ratio. Pellets (2.2 g.) were manufactured in a ½ inch diameter steel die at 10 ton/in² for 30 seconds.

Dissolution tests were carried out in 200 ml. of stirred 0.1 N HCl at 37° C., simulating conditions in the stomach at body temperature. In standardising these conditions, it was considered necessary to investigate the effect of stirrer speed on the dissolution rate and eventually a content stirrer speed of 200 rev./min. was chosen for all tests. Analysis of samples was carried out by spectrophotometry, using the aspirin absorption peaks at 227 and 276 mμ. After the test, the pellet was rinsed with distilled water, dried and then accurately reweighed. Weight losses agreed to within 1 mg. with those estimated by spectrophotometric analysis and calibration curves.

TABLE 1:

Coating with Aspirin Polymer by Heating

Example No.	Surface Treatment	Rate of solution × 10^4 g./cm.²/min.		
		0 — 5 min.	5 — 30 min.	Relative Rate* 5 — 30 min./uncoated rate per cent
0	Aspirin itself	5.09	4.36	
1	800° C. for 2 sec.	3.84	3.55	81
2	120° C. for 20 min. in air	3.75	2.89	66
3	(Continuation of 2)	30 — 35 min. 3.82	35 — 60 min. 2.91	67

* Solubility rate of the polymer coated tablet compared with the uncoated tablet. Rate of solution of the uncoated tablet being taken as 100.

TABLE 2:

Coating with Aspirin Polymer, Ethylcellulose and Hydrophobic Compounds from Solution

Example No.	Surface Treatment				Rate of solution × 10^4 g./cm.²/min.		
	Coating	Time, Sec.	Temp. °C.	Change in weight of pellet, %	0 — 5 min.	5 — 30 min.	Relative Rate: 5 — 30 min./uncoated rate per cent
4	1% w/v aspirin polymer* in benzene. Dipped and dried in warm air twice	10	25	+0.29	3.66	2.28	52
5	As above but applied and dried twice at room temperature	10	25	+0.46	1.64	1.19	27
6	1% w/v aspirin polymer* in benzene. Dipped and dried 5 times in air at room temperature	25	25	+0.37	1.13	0.79	18
7	(Continuation of 6)				30—35 min. 1.31	30—270 min. 0.73	17
8	An aspirin pellet containing 5% crushed polymer					3.64	83

* Aspirin polymer produced by heat treatment at the melting point of aspirin.

TABLE 2 (Continued)

Example No.	Surface Treatment				Rate of solution × 10^4 g./cm.²/min.		
	Coating	Time, Sec.	Temp. °C.	Change in weight of pellet, %	0 — 5 min.	5 — 30 min.	Relative Rate: 5 — 30 min./uncoated rate per cent
9	1% w/v solution of ethyl cellulose in ethanol. Sample dipped and dried out in air at room temperature	2	25	+0.52	3.12	2.15	49
10	As above, dipped and dried five times	10	25	+0.27	0.63	0.22	5
11	0.002 M soln. of montan wax in benzene dipped and dried	10	25	+0.01	4.25	3.08	71
12	0.05 N soln. of stearic acid in methanol dipped and dried	10	25		2.12	2.00	46
13	Saturated stearic acid solution in ethanol	30	25		2.12	0.19	4

WHAT I CLAIM IS:—

1. Tablets or crystallites of aspirin coated with a polymer of aspirin as hereinbefore defined.

2. Tablets of aspirin formed from aspirin crystallites which crystallites are coated with a polymer of aspirin.

3. Tablets or crystallites of aspirin as claimed in claim 1 substantially as described with reference to any of the Examples.

4. A process for the production of coated tablets or crystallites as claimed in Claim 1 wherein tablets or crystallites of aspirin are heated to cause polymerisation of their surface.

5. A process as claimed in Claim 4 wherein crystallites are heated while in a fluidised bed.

6. A process as claimed in Claim 4 or 5 substantially as described with reference to any of Examples 1 to 3.

7. A process for the production of coated tablets or crystallites as claimed in Claim 1 wherein the tablets or crystallites are coated with a solution of the aspirin polymer in a volatile solvent, inert to aspirin and to the polymer, and the solvent is removed.

8. A process as claimed in Claim 7 wherein the solvent is benzene.

9. A process as claimed in Claim 8 substantially as described with reference to any of Examples 4 to 7.

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